various pituitary hormones; and the histaminase and pitocinase contents of the plasma rise in characteristic fashions.

In abnormal pregnancies comparatively few hormone studies have been made except in toxaemia and abortion. In the former it seems that most, but not all, cases show an increase in chorionic gonadotrophin and a decrease in oestrogens and pregnanediol; probably the adrenal corticoids are also increased, though the 17-ketosteroids are decreased. In threatened abortion there is usually, but certainly not always, a low pregnanediol excretion and a low serum precipitable iodine (representing circulating thyroid hormone) and histaminase content. The chorionic gonadotrophin is greatly increased in hydatidiform mole and in chorion epithelioma. Less well-defined hormone changes may be found in various other abnormalities of pregnancy.

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The international conference on blood transfusion, recently held at the British Standards Institution in London, reached agreement on several fundamental proposals, the objectives of which are to get standardization and interchangeability of the equipment involved both in obtaining blood from donors and in giving transfusion to patients. Among the proposals agreed, and which it is expected will be the subject of International Organization for Standardization recommendations for national standards, are such important items as: overall sizes of glass containers, including sizes of the necks of the bottles; properties to be possessed by the stoppers of the bottles; the dimensions of the mounts for flexible tubing and piercing-needles; identification of the piercing positions in the stoppers separately for collecting and for transfusion of blood; minimum rate of filter and drip chamber flow. Items for future study include: standard sizes of the most used bottle; type of mount for hypodermic needle; simple label identification of the blood group of the contents of the bottle, and performance standards for the glass bottles.

CHANGES IN BASAL METABOLISM, SERUM-PROTEIN-BOUND IODINE, AND CHOLESTEROL DURING TREATMENT OF HYPOTHYROIDISM WITH ORAL THYROID AND L-THYROXINE SODIUM

BY

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It has been generally established that in patients with untreated hypothyroidism the serum-protein-bound iodine (P.B.I.) is consistently below the normal range of 4 to 8 μg. per 100 ml., and the literature has been reviewed by Rapport and Curtis (1950). Further, Winkler, Riggs, and Man (1945) claimed that serum iodine is not only a valuable aid in the diagnosis of hypothyroidism but a useful criterion of the adequacy of treatment with thyroid substance, for its return to within the normal range with adequate treatment is a better indication of the thyroid status of the patient than the basal metabolic rate (B.M.R.), the latter becoming stabilized at a slower rate than the serum iodine.

In support of this statement Winkler *et al.* described their findings, first, in a case of post-operative hypothyroidism, after thyroidectomy for thyrotoxicosis: "Forty days after operation the serum iodine had already fallen to 1 μg. per 100 ml., yet the metabolic rate was still + 3%; and, secondly, their observations in controlled hypothyroidism after withholding thyroid: "Indeed, in the entire series of patients at the time of the initial iodine determination, metabolic rates as low as −30% or less need not appear unless the patient had remained untreated for several years." They also quoted the case of a patient with hypothyroidism whose initial (untreated) B.M.R. was −34, and who after more than a year of adequate thyroid therapy maintained a normal B.M.R. of −6, despite a period of over eight months without thyroid, and a serum iodine of 2.6 μg. per 100 ml. It has also been stated that the latter is less subject than the B.M.R. to fluctuations in serial determination (Riggs, 1947). Hypercholesterolaemia is usually another characteristic feature of hypothyroidism, but it is not apparently an obligatory accompaniment (Winkler, Riggs, and Man, 1945).

The treatment of hypothyroidism with synthetic thyroxine has been described by Hart and Maclagan (1950), who conclude that L-thyroxine sodium is as satisfactory for the purpose as thyroid extract, and suggest that it has an advantage in reliability in that it is a synthetic substance and requires no biological or chemical standardization.

In order to compare the results of treatment of hypothyroidism with L-thyroxine sodium and with whole dried thyroid we have made serial examinations of five established cases. The patients voluntarily agreed to stop treatment for a period of some two months, after

which time the B.M.R., P.B.I., and serum cholesterol were determined while these substances were given for alternating periods.

Methods

The B.M.R. was measured by the closed-circuit method, evidence of the accuracy of which was given by Robertson (1937). The apparatus used was the Benedict–Roth with recording kymograph. All machines were alcohol-checked (Barrett and Robertson, 1937) and found to be accurate; in addition each was checked once a week by a model whose B.M.R. was in the region of 54 calories an hour. The standard technique used in measuring the B.M.R. has been described by Robertson (1944). The subjects attended on at least two successive mornings, and were seen personally by one of us. If on the second day the duplicates agreed within 5% (and were not higher than the first-day readings) the lower reading was taken as the B.M.R. On the other hand, if the duplicate readings were not within 5%, or the second-day readings were higher than those on the first day, then readings were taken on subsequent days until a constant reading was obtained.

In the present series, excluding the initial readings, basal rates were obtained in two days. As the technique for measuring the basal metabolism varies in different laboratories (DuBois, 1936), it is important, particularly when comparing the B.M.R. with the serum iodine, to describe precisely the technique employed and the chemical procedure adopted in estimating the blood iodine. The P.B.I. was determined by the method of Barker (1948) as modified by Barker and Lipner (1949), with some modifications which will be discussed elsewhere (Kirkpatrick—unpublished). Cholesterol was estimated by the method of Sackett (1925). Medication was given orally in the form of tablets—L-thyroxine sodium (Glaxo), 0.1 mg., or thyroid *B.P.*, 1 gr. (65 mg.) (Armour)—also gelatin-coated tablets of a thyroid preparation stated to be of *B.P.* specification.

Results

The detailed results of our investigations are conveniently shown in Figs. 1–5. In each case, after a period on L-thyroxine sodium with increasing dosage, thyroid was substituted in the form of gelatin-coated tablets. The net result was a general return to a near myxoedematous condition regardless of dose. Upon investigating the disintegration characteristics of these tablets it was found that only a small indefinite proportion disintegrated at all under physiological conditions, and the results have been disregarded except in the qualitative sense of confirming a lag in the response of the B.M.R. to a change of thyroid status, and in disclosing the hazard of using tablets not of *B.P.* specification.

The following changes have been noted from a study of the charts.

P.B.I.—A rapid rise occurs at the initiation of treatment, and the level rises or falls with variations in dosage, being stabilized within two weeks on a fixed dose irrespective of whether thyroxine or thyroid is being administered. Cessation of treatment in each case reduced the level of the P.B.I. to well below the range of our normal controls—namely, 3.6 to 8.6 μg. per 100 ml.

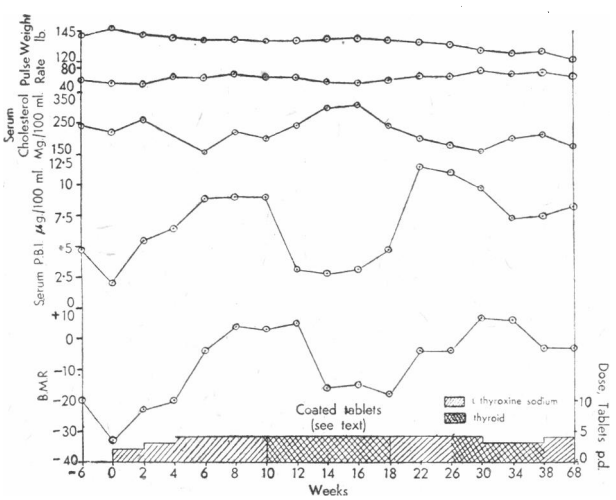

FIG. 1.—Observations on Case 1.

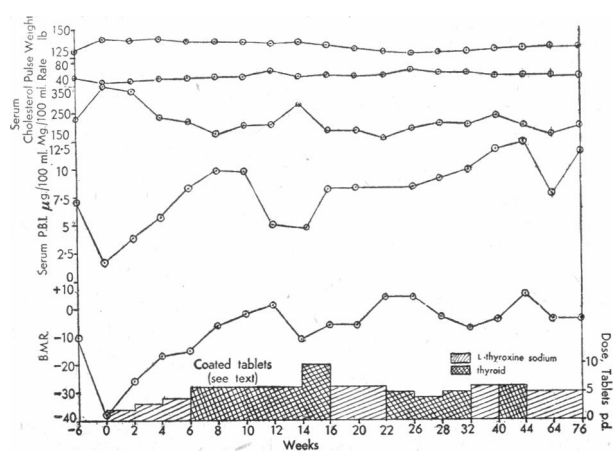

FIG. 2.—Observations on Case 2.

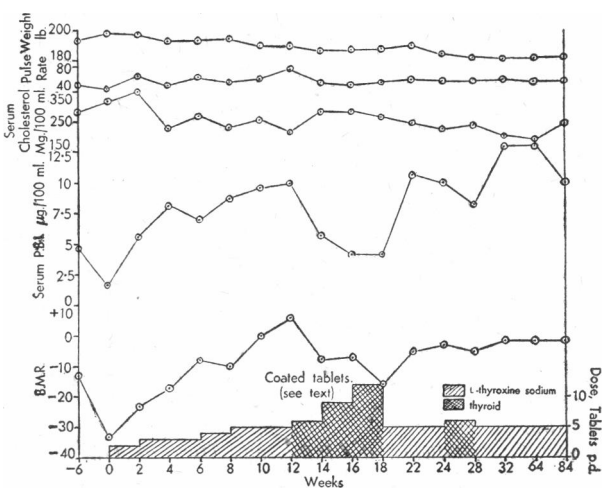

FIG. 3.—Observations on Case 3.

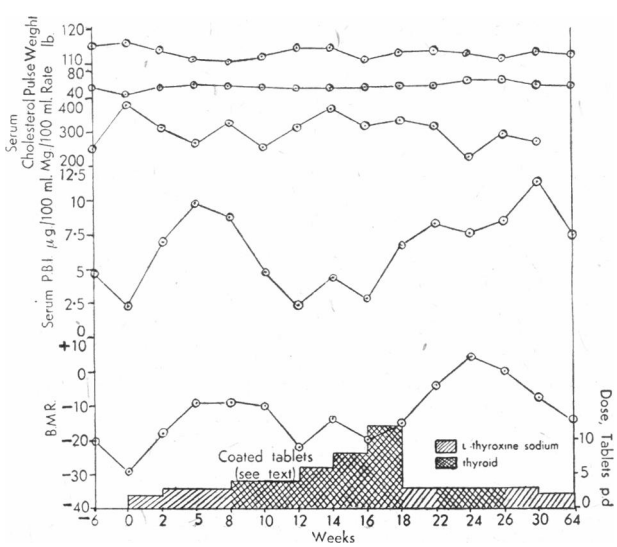

FIG. 4.—Observations on Case 4.

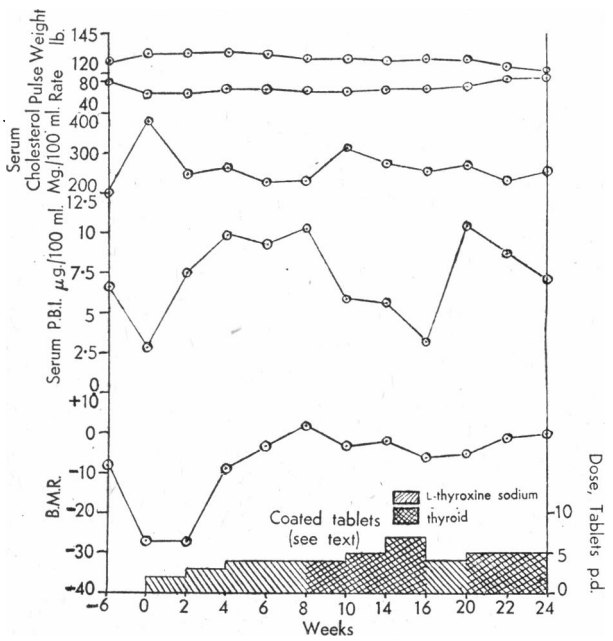

FIG. 5.—Observations on Case 5.

B.M.R.—There is a distinct lag in the response of the B.M.R. both to initiation of treatment and to changes in the latter which involve a significant change in the P.B.I. This lag may take the form of a steady decrease or increase until stabilization occurs, or it may even result in no change in the B.M.R. during the first two weeks. Stabilization of the B.M.R. is not complete until four weeks have elapsed on a fixed dosage.

Cholesterol.—In each of our five cases hypercholesterolaemia was present coincident with myxoedema. During treatment the cholesterol level gave a fair indication of the thyroid status, though the changes incline to sluggishness compared with the P.B.I., and some rather inexplicable changes seem liable to occur.

Calculations from our results have been made of the direct relationships between the P.B.I., B.M.R., and doses of thyroxine or thyroid, and the findings are summarized below.

Relation Between the P.B.I. and Dose of Thyroxine or Thyroid (Tables I and II).—The calculation has been made by dividing the observed rise in P.B.I. in µg. per 100 ml. from the basic untreated level by the dose.

Relation Between the B.M.R. and Dose of Thyroxine or Thyroid (Tables III and IV).—In correlating the B.M.R. with the dose of medicant, it is obviously necessary to allow enough time for stabilization of the former. We have accordingly employed only those figures that were obtained after four weeks at the set dosage. Calculation was made by dividing the rise from the basic untreated level by the dose.

Relation Between the P.B.I. and B.M.R. (Table V).—This relationship was calculated by dividing the rise in B.M.R. from the untreated basic level to a stabilized value by the corresponding rise in P.B.I. from the untreated basic level.

TABLE I.—*Rise in P.B.I. (µg. per 100 ml.) per 0.1 mg. L-thyroxine Sodium*

Patient	1	2	3	4	5
Individual mean	1·7	1·4	2·1	2·4	2·2

Mean of all results = 1·9. Standard deviation, ±0·30.

TABLE II.—*Rise in P.B.I. (µg. per 100 ml.) per 1 gr. (65 mg.) Thyroid*

Patient	1	2	3	4	5
Individual mean	2·1	1·7	1·1	1·6	1·3

Mean of all results = 1·7. Standard deviation, ±0·58.

TABLE III.—*Rise in B.M.R. (%) per 0.1 mg. L-thyroxine Sodium*

Patient	1	2	3	4	5
Individual mean	9	7	7	6	7

Mean of all results = 7. Standard deviation, ±1·2.

TABLE IV.—*Rise in B.M.R. (%) per 1 gr. (65 mg.) Thyroid*

Patient	1	2	3	4	5
Individual mean	13	8	5	9	6

Mean of all results = 9. Standard deviation, ±3·2.

TABLE V.—*Rise in B.M.R. % per 1 µg. % Rise in P.B.I.*

(*a*) *Treatment with L-thyroxine Sodium*

Patient	1	2	3	4	5
Individual mean	5·0	4·7	4·2	3·5	3·9

Mean of all results = 4·4. Standard deviation, ±0·55.

(*b*) *Treatment with Thyroid*

Patient	1	2	3	4	5
Individual mean	5·4	4·3	4·8	5·2	4·5

Mean of all results = 5·0. Standard deviation, ±0·77.

Table VI shows the decline in the B.M.R. after treatment with thyroid was discontinued. Symptoms of hypothyroidism were complained of after three weeks and signs were apparent by the fifth week. By five to eight weeks after thyroid had been discontinued the B.M.R. had practically fallen to the initial level when the patient was first seen and before any treatment had been instituted. The serum iodine also decreased after thyroid had been stopped.

TABLE VI.—*Fall in B.M.R. and P.B.I. After Omitting Thyroid for Five to Eight Weeks in Established and Treated Cases of Myxoedema. Basal Metabolism: Normal Range 0 to −20 (Standards of Aub and DuBois)*

Patient	Untreated Initial Observations			Present Investigations									Present Maintenance Dosage of Thyroid and Thyroxine					
				Adequately Treated with Thyroid					After Thyroid Omitted									
	Date	B.M.R.	Cholesterol mg./100 ml.	Thyroid gr. per Day	Years on Thyroid	B.M.R.	P.B.I. µg./100 ml.	Cholesterol mg./100 ml.	Days off Thyroid	B.M.R.	P.B.I. µg./100 ml.	Cholesterol mg./100 ml.	Thyroid gr. per Day	Thyroxine mg. per Day	B.M.R.	P.B.I. µg./100 ml.	Cholesterol mg./100 ml.	Age
1	1941	−29	325	2	9	−16	4·8	246	21 33	−25 −33	2·0	220	3	0·3	−3	8·3	165	62
2	1942	−40	265	4	9	−10	7·1	230	41	−38	1·7	350	5	0·5	−4	11·5	170	49
3	1942	−37	535	6	8	−13	4·5	286	36	−33	1·6	318	6	0·5	−2	10·0	180	51
4	1936	−28	330	1	14	−20	4·7	240	42 58	−24 −29	3·6 2·3	255 382	2	0·2	−12	7·4	220	63
5	1942	−30	415	3	8	−9	6·6	196	21 35	−24 −27	2·8	380	5	0·4	−1	6·4	232	66
Mean		−33	374			−18	5·5	239		−32	2·1	330			−4	8·3	193	

Discussion

When thyroid was withheld from cases of hypothyroidism the B.M.R. fell and in five to eight weeks reached the low level found before treatment. There was a parallel fall in the serum iodine over the same period. These observations do not agree with those reported by Winkler, Riggs, and Man (1945), who stated that the decrease in serum iodine "may take place weeks or months before there is any marked change in the basal metabolism." The decline in the B.M.R. to an athyreotic level, as we have reported after withholding thyroid for five to eight weeks in cases of treated hypothyroidism, would be expected from the work of Boothby and his co-workers (1924, 1925) on the calorigenic properties of a single injection of thyroxine in cases of hypothyroidism, when they found that the thyroxine was destroyed or eliminated in about fifty days.

Some confusion may be caused by the following statement in Winkler, Riggs, and Man's paper (1945): "In the entire series of patients at the time of the initial iodine determinations metabolic rates of −30 or lower need not appear for several years." By analogy this might be understood to imply that these authors regarded a B.M.R. of at least −30 as a prerequisite for the diagnosis of untreated hypothyroidism. In thyrotoxicosis there is no absolute basal rate figure for confirming the diagnosis because, although the B.M.R. may be well above +50 in severe cases, in mild cases it may lie within the normal range (Robertson, 1934), and such findings in reverse could equally well apply to cases of hypothyroidism. Means (1948) has stated that in complete athyreosis the B.M.R. runs very constantly in most cases between −35 and −45, and here the clear-cut picture of myxoedema is present; but in lesser degrees of hypothyroidism correspondingly higher basal rates will be obtained, and these may even border on the lower limits of the normal range.

The specific action of iodine on the B.M.R. in thyrotoxicosis has been employed as a delicate and exact diagnostic aid in that condition when the degree of toxicity is mild and clinically the picture is difficult to assess (Means, 1933; Robertson, 1934); and Robertson (1949) has suggested that the effect of thyroid, 2 gr. (130 mg.) daily, on the B.M.R. was of equal use in diagnosing mild hypothyroidism. To fix a B.M.R. of −35 with an average of about −40 (Means, 1948) as an arbitrary limit above which clear-cut myxoedema or complete athyreosis can be ruled out is now generally accepted, but rates higher than this need not exclude milder degrees of hypothyroidism. In addition to this being a personal experience, a study of Winkler, Riggs, and Man's cases (1945) shows that 13 out of 18 untreated cases of hypothyroidism had an initial B.M.R. higher than −35, and three were as high as −18 to −19. It is difficult to explain, as described by the above authors, a B.M.R. of −6 after stopping thyroid, 1½ gr. (100 mg.), for over eight months in a case with an initial B.M.R. of −34. No such phenomenon has been noted in a series of 16 cases of established myxoedema with a mean initial B.M.R. of −40 (range −34 to −47). In all cases the B.M.R. fell from normal to the initial level within two months of stopping thyroid (Robertson, unpublished results).

Our general observations on the changes in the B.M.R. and P.B.I. during treatment of hypothyroidism are in substantial agreement with those of Winkler, Riggs, and Man (1945), in that there is a rapid stabilization of the P.B.I. during treatment compared with a lag in the response of the B.M.R. Our calculations correlating the changes in the B.M.R. with those in the P.B.I., and the changes in the P.B.I. and B.M.R. with the dose of thyroxine or thyroid, have been confined to the simplest terms, but the inferences to be drawn from the results appear to us to be quite clear-cut. Tables I and II indicate that the variation in the response of the P.B.I. to thyroid is twice as great as that to L-thyroxine sodium. Tables III and IV show the response of the B.M.R. to thyroid to be about two and a half times as variable as that to L-thyroxine sodium. In contrast to these observations Table V shows that correlation of the B.M.R. with P.B.I. is of the same order irrespective of whether thyroid or L-thyroxine is administered. It therefore seems obvious that a large part of the variation encountered in the use of thyroid for the control of hypothyroidism can be attributed to deviations in the biological potency of the thyroid, and that this particular variation can be avoided by administration of L-thyroxine sodium.

The lag in the B.M.R. behind the P.B.I. led Winkler, Riggs, and Man (1945) to state that fluctuation in P.B.I. in hypothyroidism was a more useful criterion than the B.M.R. of the adequacy of treatment with thyroid. Our results do not support this view. Next to the clinical picture we feel that the B.M.R. gives a better index of the patient's thyroid requirements than the P.B.I., for on several occasions during thyroid and thyroxine medication the P.B.I. reached levels commonly found in thyrotoxicosis (above 8 μg. per 100 ml.) when in fact clinically there was no evidence of overdosage and the B.M.R. was within the normal range.

Summary and Conclusions

Five cases of hypothyroidism have been treated orally with L-thyroxine sodium and two brands of thyroid over periods of six to eighteen months.

Clinically, L-thyroxine sodium is as satisfactory as thyroid gland in the treatment of hypothyroidism.

Relationships between the B.M.R., serum iodine, and doses of thyroid and L-thyroxine sodium observed during treatment of five cases of hypothyroidism indicate a less variable response to thyroxine than to thyroid. Treatment with L-thyroxine sodium results in an average rise of 1.9 μg. per 100 ml. in the protein-bound iodine (P.B.I.) and 7% in the B.M.R. per 0.1-mg. dose.

Stabilization of the P.B.I. occurs more rapidly than that of the B.M.R. during treatment with either L-thyroxine sodium or thyroid. Next to the clinical picture the B.M.R. gives a better index of the patient's thyroid or thyroxine requirements than the P.B.I., for on several occasions during therapy the P.B.I. reached levels commonly found in thyrotoxicosis (above 8 μg. per 100 ml.) when clinically there was no evidence of overdosage and the B.M.R. was within the normal range. The P.B.I. tended to reach higher values with thyroxine than with equivalent doses of thyroid.

Our results, although on a small series of patients, do not support the statement of Means (1948) that the maintenance ration of thyroid is remarkably similar from patient to patient. In our series, dosages of from 0.2 to 0.5 mg. of thyroxine daily, or approximately 2 to 5 gr. (130 to 325 mg.) of thyroid daily, were required to keep the patients symptom-free.

Winkler, Riggs, and Man's statement (1945) that patients are unable to tolerate more than 3 gr. (200 mg.) of thyroid daily without developing symptoms of overdosage is also not supported. The restoration of a P.B.I. to a normal level of 6 μg. per 100 ml. as suggested by these authors was found to be no guide to assessing the maintenance dose of thyroid; for, in our series, patients were symptom-free and without any evidence of thyroid excess at P.B.I. levels all in excess of 6 μg. per 100 ml.

Some disparity in the results can no doubt be attributed to the different methods of standardizing thyroid *B.P.* and thyroid *U.S.P.* The former is assayed for thyroxine iodine and the latter for total iodine, the standards being 0.1% and 0.2% respectively, so that unless the ratio of thyroxine iodine to total iodine has a constant value of 1:2, there must obviously be a difference in biological activity.

The serum cholesterol affords an approximate indication of thyroid status, but seems liable to unaccountable fluctuations.

It is a pleasure to thank Mr. A. V. Bridgland, Chairman of the Trustees of the London Clinic, for granting facilities for this investigation. The thyroxine derivative used was generously supplied by Glaxo Laboratories Ltd.

ADDENDUM.—Subsequent to the completion and submission for publication of this paper, further proof of one of our conclusions has been rather strikingly afforded. One of the patients (No. 3) was referred to us for re-examination by her local doctor one year after stabilization on L-thyroxine sodium, 0.5 mg. daily, with the opinion that, clinically, she appeared in need of a higher dosage of thyroxine. Our examination showed her B.M.R. to be well within the normal range (−3), whereas her serum P.B.I. was 13.5 μg.%, a distinctly thyrotoxic level. It seems obvious, therefore, that during treatment of hypothyroidism with thyroxine the serum P.B.I. may reach a high level indicative of thyrotoxicosis when no such condition is present clinically, and that a more accurate indication of clinical status is provided by the B.M.R.

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A PERSISTENT URINARY SALMONELLA DUBLIN CARRIER WITH BILHARZIASIS

BY

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Attention has recently been drawn to the prevalence in Egypt of urinary typhoid and paratyphoid carriers (Morton, 1949; Neva, 1949; Walton, 1949; Archer *et al.*, 1950). Their importance to the public health is attested by the fact that at least one large outbreak of typhoid among British Service men in the Suez Canal zone has been attributed to an Egyptian urinary excreter of typhoid bacilli (Anderson and Richards, 1948).

In a collaborative study with Dr. J. Weir, representative in Egypt of the Rockefeller Foundation, 53 native urinary salmonella carriers have been followed up for over a year. The distribution of these carriers by salmonella types, when they were originally detected, was as follows: 28 *Salm. typhi*, 13 *Salm. paratyphi A*, 2 *Salm. paratyphi B*, 9 *Salm. paratyphi C* (or group C), and 1 *Salm. dublin*. Some of the temporary carriers later acquired a urinary or faecal species of salmonellosis different from the original infection.

That the series should contain a carrier who has continued to excrete *Salm. dublin* in his urine for over a year seems worthy of record, because this organism is a common cause of disease in man and animals in many parts of the world, but does not appear to have been isolated in Egypt before. Cattle are apparently the main reservoir of infection and the usual source of the human disease, but the present case indicates that the human carrier may play a more important part in the dissemination of *Salm. dublin* infection than has hitherto been thought.

Case Report

This man, an agricultural labourer aged about 35, was found in a bacteriological survey of the general population of a Nile Delta village, where the urinary enteric carrier rate among men, women, and children was 3% (Miller, 1949). He is physically fit, and his only admitted incapacitating illness was one month's "fever" about 10 years previously. He had been passing blood in his urine for 15 to 20 years, but this did not trouble him and he had never sought treatment for schistosomiasis. His youngest child died of "enteritis" at the age of 1 year, but there was no other history of serious family illness. All of 18 specimens of urine examined at more or less regular intervals from November, 1949, until March, 1951, produced a heavy growth of a non-lactose fermenting organism when plated directly on Difco SS agar.

The Organism.—All isolates were actively motile Gram-negative bacilli which fermented glucose, mannite, and dulcite with the production of gas, and caused no change in lactose, sucrose, or salicin. They produced abundant hydrogen sulphide but were indole- and urea-negative and did not liquefy gelatin. They agglutinated strongly in salmonella O serum of group A, to a lesser extent in sera of groups B and D, and not at all in serum of group C; but formalinized broth cultures failed to agglutinate in any of the enteric group diagnostic H sera available in this laboratory. A culture was sent to Commander L. A. Barnes, of the Naval Medical Research Institute, Bethesda, Maryland, U.S.A., who identified the organism as *Salm. dublin*.

Eggs of *Schistosoma haematobium* were found in 16 of the 18 urine specimens, blood in 15, and macroscopic pus in every one. No salmonella or shigella organisms were cultured from 13 stool specimens examined at approximately monthly intervals.

Ten specimens of the carrier's blood were collected during the course of a year. The clots were cultured by a technique known to give a very high proportion of positive results in cases of enteric fever, but all were sterile. The serum specimens were used for agglutination tests. No H agglutinins for typhoid or paratyphoid A were detected; but low-titre (1:5–1:20) H-specific agglutinins for paratyphoid B and C were present in some of the specimens. The typhoid O titre fluctuated between 1:40 and 1:320, and the Vi titre from traces of agglutination at 1:5 or 1:10 dilutions to full standard agglutination at 1:20. The patient's serum invariably agglutinated formalinized broth cultures of his own organism at dilutions varying from 1:640 to 1:2,560.

Comment

The geographical and zoological distribution of the different salmonella species is of considerable interest and practical importance, because all seem to be potentially pathogenic for man. Although *Salm. dublin* has been isolated from many different animals, it appears to be particularly common in cattle and foxes, being at times the cause of epizootics in their young, with a high mortality leading to serious economic loss. It has been reported as a predominant salmonella type of cattle in Britain, Holland, Finland, Sweden, Australia, South Africa, and South